Currently Pending Claims

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (Currently amended) A compound of the structure or formula S-$(L)_n$-B wherein:

(a) S is an amino terminal signaling functional domain of PTH;

(b) L is a linker molecule present n times; [[and]]

(c) n is an integer greater than 1; and

(d) B is a carboxy terminal binding domain of PTH(1-34) or PTHrP(1-34), wherein said carboxy terminal binding domain binds to a PTH- receptor 1 molecule

wherein said compound ~~has a biological activity substantially similar to PTH(1-34) or PTHrP(1-34)~~ stimulates intracellular accumulation of cyclic cAMP; and

wherein $(L)_n$ ~~said linker is selected from the group comprising an~~ is n repeats of the same amino acid ~~and an aliphatic diamine~~.

2. (Original) The compound of claim 1, wherein said compound is an isolated polypeptide.

3. canceled.

4. (Original) The isolated polypeptide of claim 2, wherein S is selected from the group consisting of PTH(1-9) (AlaValSerGluIleGlnLeuMetHis) (SEQ ID NO: 1), PTH(1-5) (AlaValSerGluIle) (SEQ ID NO: 4) or PTH (1-11) (AlaValSerGluIleGlnLeuMetHisAsnLeu) (SEQ ID NO: 46).

5. (Previously presented) The isolated polypeptide of claim 2, wherein L is selected from the group consisting of Gly_5, Gly_7 and Gly_9.

6. (Previously presented) The isolated polypeptide of claim 2, wherein B is selected from the group consisting of PTH(15-31) (LeuAsnSerMetGluArgValGluTrpLeuArgLysLys LeuGlnAspVal) (SEQ ID NO:2), PTH(17-31) (SerMetGluArgValGluTrpLeuArgLysLysLeu

GlnAspVal) (SEQ ID NO:63), PTHrP (15-31) (IleGlnAspLeuArgArgArgPhePheLeuHisHis LeuIleAlaGluIle) (SEQ ID NO:8), and PTHrP(17-31) (AspLeuArgArgArgPhePheLeuHisHis LeuIleAlaGluIle) (SEQ ID NO:12).

7. (Previously presented) The isolated polypeptide of claim 2 selected from the group consisting of PG5: AlaValSerGluIleGlnLeuMetHisGlyGlyGlyGlyGlyLeuAsnSerMetGluArg ValGluTrpLeuArgLysLysLeuGlnAspVal (SEQ ID NO:3), PG9: AlaValSerGluIleGly Gly GlyGlyGlyGlyGlyGlyGlyLeuAsnSerMetGluArgValGluTrpLeuArgLysLysLeuGlnAspVal (SEQ ID NO:5), PG7: AlaValSerGluIleGlnLeuMetHisGlyGlyGlyGlyGlyGlyGlySerMetGlu ArgValGluTrpLeuArgLysLysLeuGlnAspVal (SEQ ID NO:6), PrPG5: AlaValSerGlu HisGln LeuLeuHisGlyGlyGlyGlyGlyIleGlnAspLeuArgArgArgPhePheLeuHisHisLeuIleAlaGluIle (SEQ ID NO:64), PrPG9: AlaValSerGluHisGlyGlyGlyGlyGlyGlyGlyGlyGlyIleGlnAspLeu ArgArgArgPhePheLeuHisHisLeuIleAlaGluIle (SEQ ID NO:65) and PrPG7: AlaValSer Glu HisGlnLeuLeuHisGlyGlyGlyGlyGlyGlyGlyAspLeuArgArgArgPhePheLeuHisHisLeuIleAla GluIle (SEQ ID NO:66) ~~and functional derivatives thereof~~.

8. (Previously presented) The isolated polypeptide of claim 2 selected from the group consisting of PG5: AlaValSerGluIleGlnLeuMetHisGlyGlyGlyGlyGlyLeuAsnSerMetGluArg ValGluTrpLeuArgLysLysLeuGlnAspVal (SEQ ID NO:3), PG9: AlaValSerGluIleGlyGlyGly GlyGlyGlyGlyGlyGlyLeuAsnSerMetGluArgValGluTrpLeuArgLysLysLeuGlnAspVal (SEQ ID NO:5), PG7: AlaValSerGluIleGlnLeuMetHisGlyGlyGlyGlyGlyGlyGlySerMetGluArgVal GluTrpLeuArgLysLysLeuGlnAsnVal (SEQ ID NO:6), ~~and functional derivatives thereof~~.

9. (Original) The isolated polypeptide of claim 8 wherein there is a single amino acid substitution.

10. (Previously presented) The isolated polypeptide of claim 2, wherein:

(a) S is X Val X Glu X X X X His (SEQ ID NO: 42), wherein X is an amino acid; and

(b) L is 5-10 glycine residues.

11. (Previously presented) The isolated polypeptide of claim 2, wherein:

(a) S is Ser Val Ser Glu Ile Gln Leu Met His (SEQ ID NO: 44);

(b) L is 5-10 glycine residues; and

(c) B is Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO: 45).

12. Cancelled.

13. Cancelled.

14. (Previously presented) The isolated polypeptide of claim 2, encoded by a nucleic acid sequence selected from the group consisting of: SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

15. (Withdrawn) An isolated nucleic acid sequence encoding the polypeptide of any one of claims 2-13.

16. (Withdrawn) An isolated polypeptide of the structure of formula R_1-S-$(L)_n$-R, or S-$(L)_n$-R wherein:

(a) R_1 is the PTH-1 receptor signal sequence;

(b) S is an amino-terminal ligand signaling peptide;

(c) L is a linker molecule present n times, where n is a positive integer 1-10, most preferably 4; and

(d) R is PTH-1 receptor sequence or a portion of the receptor sequence.

17. (Withdrawn) The isolated polypeptide of claim 16, wherein R_1 is the PTH-1 receptor(1-25) peptide, S is the PTH(1-9) peptide, L is Gly, wherein N is 4; and R is the PTH-1 receptor (182-end).

18. (Withdrawn) The isolated polypeptide of claim 16 having the formula S-$(L)_n$-R, wherein the R_1 moiety has been cleaved.

19. (Withdrawn) An isolated nucleic acid sequence encoding the polypeptide of claim 16.

20. (Withdrawn) An isolated polypeptide of the formula S-R, wherein:

(a) S is an amino-terminal signaling polypeptide; and

(b) R is a carboxy-terminal receptor polypeptide.

21. (Withdrawn) The isolated polypeptide of Claim 20, wherein S is the amino-terminal signaling polypeptide X Val X Glu X X X X His, wherein X is an amino acid.

22. (Withdrawn) An isolated polypeptide comprising a sequence selected from the group the of sequences consisting of SEQ ID NO: 37, SEQ ID NO:39 and SEQ ID NO: 41.

23. (Withdrawn) An isolated nucleic acid sequence encoding a polypeptide sequence of claim 22.

24. (Withdrawn) An isolated nucleic acid sequence selected from the group consisting of SEQ ID NO:36, SEQ ID NO:38 and SEQ ID NO:40.

25. (Withdrawn) An isolated nucleic acid sequence, wherein said sequence is at least 95% identical to or binds under stringent conditions to a sequence of claim 24.

26. (Withdrawn) A recombinant vector comprising a nucleic acid sequence of claim 15

27. (Withdrawn) A recombinant host cell comprising the DNA of claim 26.

28. (Withdrawn) A recombinant vector comprising a nucleic acid sequence of claim 23.

29. (Withdrawn) A recombinant host cell comprising the DNA of claim 28.

30. (Withdrawn) A method for treating mammalian conditions characterized by decreases in bone mass, wherein said method comprises administering to a subject in need thereof an effective bone mass-increasing amount of the polypeptide of any one of claims 2, 16 or 20.

31. (Withdrawn) A method for determining rates of bone reformation, bone resorption and/or bone remodeling comprising administering to a patient an effective amount of a polypeptide of any one of claims 2, 20 or 40 and determining the uptake of said peptide into the bone of said patient.

32. (Withdrawn) The method of claim 30, wherein said effective bone mass-increasing amount of said peptide is administered by providing to the patient DNA encoding said peptide and expressing said peptide *in vivo*.

33. (Withdrawn) The method of claim 32, wherein the condition to be treated is osteoporosis.

34. (Withdrawn) The method of claim 24, wherein the effective amount of said polypeptide for increasing bone mass is from about 0.01 μg/kg/day to about 1.0 μg/kg/day.

35. (Withdrawn) A method of treating diseases and disorders associated with decreased Tether1 activity comprising administering an effective amount of the polypeptide of any one of claims 2, 20 or 40, or an agonist thereof to a patient in need thereof.

36. (Withdrawn) A method of increasing cAMP in a mammalian cell having PTH-1 receptors, comprising contacting said cell with a sufficient amount of the polypeptide of any one of claims 2, 20 or 40 to increase cAMP.

37. (Original) The isolated polypeptide of claim 2 wherein B is 10-20 amino acids in length.

38. (Withdrawn) A method for screening for a peptide or non-peptide PTH agonist comprising:

(a) binding a polypeptide of claim 16 to a potential agonist; and

(b) isolating said potential agonist from said polypeptide.

39. (Withdrawn) The method of claim 38, wherein said polypeptide is Tether 1 or rδNt.

40. (Withdrawn) An isolated polypeptide, wherein said polypeptide is obtained by the method of claim 38.

41. (Previously presented) The compound of claim [[1]] 43, wherein said aliphatic diamine comprises 1 to 6 carbons.

42. (Currently amended) The compound of claim 41, wherein said aliphatic diamine is selected from the group consisting of methylene diamine, ethylene diamine, propylene diamine, tetramethylene diamine, pentamethylene diamine, hexamethylene diamine, tetramethylene diamine (also known as cadaverine), pentamethylene diamine (also known as putrescine, ~~hereinafter Pu~~), and hexamethylene diamine.

43. (New) A compound of the structure or formula S-$(L)_n$-B wherein:

(a) S is an amino terminal signaling functional domain of PTH;

(b) L is a linker molecule present n times;

(c) n is an integer from 1-9; and

(d) B is a carboxy terminal binding domain of PTH(1-34) or PTHrP(1-34), wherein said carboxy terminal binding domain binds to a PTH- receptor 1 molecule;

wherein said compound stimulates intracellular accumulation of cyclic cAMP; and

wherein said linker molecule L is an aliphatic diamine.

44. (New) The isolated polypeptide of claim 7, wherein said polypeptide is modified to improve the solubility, absorption, or biological half-life of said polypeptide and wherein said modification is selected from the group consisting of the addition of C_{1-12} alkyl groups, the addition of C_{1-12} hydroxyalkyl groups, the addition of acyl groups, and lactam cyclization.

45. (New) The isolated polypeptide of claim 8, wherein said polypeptide is modified to improve the solubility, absorption, or biological half-life of said polypeptide and wherein said modification is selected from the group consisting of the addition of C_{1-12} alkyl groups, the addition of C_{1-12} hydroxyalkyl groups, the addition of acyl groups, and lactam cyclization.

46. (New) The isolated polypeptide of claim 1, wherein n is an integer from 5 to 9.